

General

Guideline Title

Hydroxyurea therapy in the management of sickle cell disease. In: Evidence-based management of sickle cell disease.

Bibliographic Source(s)

Hydroxyurea therapy in the management of sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 71-8.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the grades of recommendation (Strong, Weak), the quality of supporting evidence (High, Moderate, Low, Very Low), and consensus statements are presented at the end of the "Major Recommendations" field.

Note from the National Heart, Lung, and Blood Institute (NHLBI) and the National Guideline Clearinghouse (NGC): The evidence-based management of sickle cell disease (SCD) has been divided into five topic areas with individual summaries covering recommendations to assist health care professionals in various aspects of management. In addition to the current summary, the following are available:

- [Health maintenance for people with sickle cell disease](#)
- [Managing acute complications of sickle cell disease](#)
- [Managing chronic complications of sickle cell disease](#)
- [Blood transfusion in the management of sickle cell disease](#)

Hydroxyurea Treatment Recommendations

1. Educate all patients with sickle cell anemia (SCA) and their family members about hydroxyurea therapy (see consensus treatment protocol below). (Consensus–Panel Expertise)
2. In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, treat with hydroxyurea. (Strong Recommendation, High-Quality Evidence)
3. In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea. (Strong Recommendation, Moderate-Quality Evidence)
4. In adults with SCA who have a history of severe and/or recurrent acute chest syndrome (ACS), treat with hydroxyurea.* (Strong

Recommendation, Moderate-Quality Evidence)

5. In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea. (Strong Recommendation, Moderate-Quality Evidence)
6. In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia). (Strong Recommendation, High-Quality Evidence for ages 9–42 months; Moderate Recommendation, Moderate-Quality Evidence for children >42 months and adolescents). Note: The panel intentionally used the term "offer" realizing that patients' values and preferences may differ particularly considering treatment burden (e.g., laboratory monitoring, office visits), availability of drug in a liquid form, and cost. Therefore, the panel strongly encourages shared decisionmaking and discussion of hydroxyurea therapy with all patients.
7. In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, hydroxyurea therapy can be added to improve anemia. (Weak Recommendation, Low-Quality Evidence)
8. In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy. (Moderate Recommendation, Very Low-Quality Evidence)
9. To ensure proper use of hydroxyurea and maximize benefits and safety, use an established prescribing and monitoring protocol. (Strong Recommendation, High-Quality Evidence)
10. In people with HbSβ⁺-thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life, consult a sickle cell expert for consideration of hydroxyurea therapy. (Moderate Recommendation, Low-Quality Evidence)
11. In people not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult a sickle cell expert. (Moderate Recommendation, Very Low-Quality Evidence)

*For more information, see the ACS section of the NGC summary of the NHLBI guideline [Managing acute complications of sickle cell disease](#).

Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and red blood cell (RBC) mean corpuscular volume (MCV)
- Quantitative measurement of fetal hemoglobin (HbF) if available (e.g., hemoglobin electrophoresis, high-performance liquid chromatography [HPLC])
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring Therapy

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy.
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.
- Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease.
- Starting dosage for infants and children: 20 mg/kg/day.
- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for a target absolute neutrophil count $\geq 2,000/\mu\text{L}$; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/ μL .
- Maintain platelet count $\geq 80,000/\mu\text{L}$.
- If neutropenia or thrombocytopenia occurs:
 - Hold hydroxyurea dosing.
 - Monitor CBC with WBC differential weekly.
 - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias.
- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
 - Increase by 5 mg/kg/day increments every 8 weeks.
 - Give until mild myelosuppression (absolute neutrophil count 2,000/ μL to 4,000/ μL) is achieved, up to a maximum of 35 mg/kg/day.
- Once a stable dose is established, laboratory safety monitoring should include:
 - CBC with WBC differential, reticulocyte count, and platelet count every 2–3 months
- People should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a 6-month trial on the maximum tolerated dose is

required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.

- Monitor RBC MCV and HbF levels for evidence of consistent or progressive laboratory response.
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy.
- For the patient who has a clinical response, long-term hydroxyurea therapy is indicated.
- Hydroxyurea therapy should be continued during hospitalizations or illness.

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Strong recommendation High-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies*	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation Moderate-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation Low-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation Very low-quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.
Weak recommendation High-quality evidence	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation Moderate-quality evidence	Benefits closely balanced with harms and burdens	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation Low-quality evidence	Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and burdens	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation Very low-quality evidence	Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain.

Source: Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med*. 2006 Sep 1;174(5):605-14. Official Journal of the American Thoracic Society.

*Exceptionally strong evidence from unbiased observational studies includes: (1) evidence from studies that yield estimates of the treatment effect that are large and consistent; (2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and (3) evidence in which a dose-response gradient exists.

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

Consensus—Panel Expertise

- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).
- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with SCD presenting with fever or worsening anemia).
- Recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus—Adapted

- These recommendations were based on the panel's expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Sickle cell disease (SCD)

Guideline Category

Management

Treatment

Clinical Specialty

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Nursing

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To synthesize the available scientific evidence on sickle cell disease (SCD) and offer guidance to busy primary care clinicians
- To help people living with SCD receive appropriate care by providing the best science-based recommendations to guide practice decisions
- To assist health care professionals in the management of common issues, including routine health maintenance, the recognition and treatment of common acute and chronic complications and comorbidities of SCD, as well as the indications for and monitoring of hydroxyurea and blood transfusion therapy
- To help provide the latest evidence-based recommendations to manage this condition and to help engage health care professionals in supporting their implementation at the practice level
- To address the use of hydroxyurea (also called hydroxycarbamide) in adults and children who have SCD

Target Population

Infants, children, adolescents, and adults with sickle cell disease (SCD)

Interventions and Practices Considered

1. Hydroxyurea therapy
2. Education of patient and family about hydroxyurea
3. Laboratory tests before starting hydroxyurea
 - Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and red blood cell (RBC) mean corpuscular volume (MCV)
 - Quantitative measurement of fetal hemoglobin (HbF) if available
 - Comprehensive metabolic profile, including renal and liver function tests
 - Pregnancy test for women
4. Initiating and monitoring therapy, including dosage adjustments

Major Outcomes Considered

- Benefits of hydroxyurea
 - Death
 - Stroke
 - Pain crises
 - Need for transfusion
 - Hemoglobin

- Hemoglobin F levels
- Harms of hydroxyurea (adverse effects)
- Barriers to implementation of hydroxyurea treatment and interventions to overcome barriers
- Treatment protocols and monitoring parameters

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Literature Search

Due to the comprehensive scope of the guidelines, the search strategies for the systematic reviews were designed to have high sensitivity and low specificity; hence, the strategies were often derived from population and condition terms (e.g., people with sickle cell disease [SCD] who have priapism) and not restricted or combined with outcome or intervention terms. To be inclusive of the available literature in the field, searches included randomized trials, nonrandomized intervention studies, and observational studies. Case reports and small case series were included only when outcomes involved harm (e.g., the adverse effects of hydroxyurea) or when rare complications were expected to be reported.

Literature searches involved multiple databases (e.g., Medline® In-Process & Other Non-Indexed Citations, MEDLINE®, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature [CINAHL®], TOXLINE®, and Scopus) and used controlled vocabulary (prespecified) terms supplemented with keywords to define concept areas.

An updated search was performed to span the time from June 1, 2010 through July 11, 2014.

Guideline-specific Literature Search

For this guideline, all human studies in English published from 2007 to May 2010 that addressed the Patient, Intervention, Comparison, Outcomes, and Study Design (PICOS) question were identified. Studies published prior to 2007 were obtained from the 2008 National Institutes of Health Consensus Conference on Hydroxyurea document "Hydroxyurea for the Treatment of Sickle Cell Disease," which included a systematic review. In some cases in this guideline, a literature search was not conducted, so the panel relied on their cumulative expertise and knowledge to make recommendations; these recommendations are labeled "Consensus–Panel Expertise."

Detailed information on the search questions, search strategy, study selection process, and list of excluded studies used in this guideline can be found in the systematic review (see the "Availability of Companion Documents" field).

Number of Source Documents

General Literature Search

The initial literature searches performed to support these guidelines yielded 12,532 references. The expert panel also identified an additional 1,231 potentially relevant references. An updated search of randomized controlled trials (RCTs) added eight trials. All abstracts were reviewed independently by two reviewers using an online reference management system (DistillerSR—<http://systematic-review.net>) until reviewers reached adequate agreement ($\kappa \geq 0.90$). A total of 1,575 original studies were included in the evidence tables.

Guideline-specific Literature Search

A total of 414 studies were included.

Methods Used to Assess the Quality and Strength of the Evidence

Rating Scheme for the Strength of the Evidence

See the "Rating Scheme for the Strength of the Recommendations" field.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Methodology

Evidence Synthesis

Methodologists developed evidence tables to summarize individual study findings and present the quality of evidence (i.e., confidence in the estimates of effect). The tables included descriptions of study population, sickle cell disease (SCD) genotypes, interventions, and outcomes. Additional methodological details are discussed in each evidence table, including the search question, search strategy, study selection process, and list of excluded studies (see the "Availability of Companion Documents" field).

Evidence Framework

The methodology team used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to grade the quality of evidence, and, in concert with the panel, determine the strength of recommendations. The GRADE framework is accepted by more than 75 national and international organizations (see exhibit 3 in the original guideline document). It provides the advantages of: (a) separately judging the quality of supporting evidence and strength of recommendations, and (b) incorporating factors other than evidence in decisionmaking (e.g., the balance of benefits and harms; the perceived values and preferences of those with SCD; resources; and clinical and social context). GRADE emphasizes the use of patient-important outcomes (i.e., outcomes that affect the way patients feel, function, or survive) over laboratory and physiologic outcomes.

Determining Evidence Quality

In the GRADE framework, the quality of evidence (in this case, the body of evidence) is rated as high, moderate, low, or very low. The quality of evidence derived from randomized trials starts as "high," and the quality of evidence derived from observational studies starts as "low." The quality of evidence can then be lowered due to methodological limitations in individual studies (risk of bias), inconsistency across studies (heterogeneity), indirectness (the extent to which the evidence fails to apply to the specific clinical question in terms of the patients, interventions, or outcomes), imprecision (typically due to a small number of events or wide confidence intervals), and the presence of publication and reporting biases. Conversely, the quality of evidence can be upgraded in certain situations such as when the treatment effect is large or a dose-response relationship is evident.

Existing Systematic Reviews and Clinical Practice Guidelines

The expert panel and methodology team identified existing systematic reviews and clinical practice guidelines that were relevant to the topics of this guideline, even though they were not necessarily specific to people with SCD. If the methodological quality of these resources was found to be appropriate by the methodology team, they were used. Using this external evidence was considered helpful because well-conducted systematic reviews made the process of identifying relevant studies more feasible. In addition, using existing guidelines developed by professional organizations enabled the panel to develop more comprehensive recommendations that addressed specific aspects of care in individuals with SCD. Usually, this external evidence was derived from studies in non-sickle cell patient cohorts because it was felt that they offered more precise and useful inferences than evidence derived from sickle cell patient studies. For example, comparative evidence in the area of pain management in people with SCD was sparse. In this situation, pain management guidelines from individuals with other pain-related conditions proved to be helpful.

The methodology team used the AMSTAR tool to assess the methodological quality of systematic reviews. Recent well-conducted systematic reviews were identified that addressed hydroxyurea therapy in pediatric and adult patients. The expert panel and methodology team appraised

these reviews and conducted additional searches to update the existing systematic review through May 2010 to find evidence for the benefits, harms, and barriers of using hydroxyurea. Regarding the management of children with SCD complications, the panel also used recent evidence that had been systematically reviewed.

Existing clinical practice guidelines were considered acceptable if they had prespecified clinical questions, were developed after a comprehensive literature search, had explicit and clear criteria for the inclusion of evidence, and included recommendations that were explicitly linked to the quality of supporting evidence. The expert panel and methodology team used relevant recommendations from the U.S. Preventive Services Task Force (USPSTF), the Advisory Committee on Immunization Practices (ACIP), the Centers for Disease Control and Prevention's (CDC) adaptation of the World Health Organization's (WHO) "Medical Eligibility Criteria for Contraceptive Use," and the American Pain Society's "Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease," and "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain."

Guideline-specific Methodology

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the evidence table in the systematic review (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These guidelines were developed by an expert panel composed of health care professionals with expertise in family medicine, general internal medicine, adult and pediatric hematology, psychiatry, transfusion medicine, obstetrics and gynecology, emergency department nursing, and evidence-based medicine. Panel members were selected by the National Heart, Lung, and Blood Institute's (NHLBI's) leadership.

Process and Methodology

The expert panel first convened in the spring of 2009 to establish the vision and purpose of the panel, discuss the process and schedule for producing the guidelines, and determine the critical areas to be addressed. Prior to this meeting, the expert panel participated in a conference call to introduce the panel's work and discuss the overarching questions that should be answered by the guidelines. Before beginning the writing of the guidelines report, the expert panel divided its work into sections dealing with preventive care or health maintenance, recognition and management of acute sickle-cell disease (SCD)-related complications, recognition and management of chronic SCD-related complications, and the two most broadly assessed and available disease-modifying therapies for SCD, hydroxyurea and chronic blood transfusions.

With the assistance of the methodology team and the supporting evidence center, the panel then developed key questions and literature search terms to identify evidence. The field of SCD has a limited number of randomized controlled trials (RCTs) or large prospective cohort studies to guide clinical decisionmaking; therefore, few of the recommendations in this document are based on this highest quality evidence. For common health issues, the panel included the evidence-based recommendations of the United States Preventive Services Task Force (USPSTF) as well as vetted recommendations of other groups. These recommendations include the SCD reproductive-related recommendations of the World Health Organization (WHO), the immunization recommendations of the Advisory Committee on Immunization Practices (ACIP), and the acute and chronic pain management recommendations of the American Pain Society (APS). These recommendations are denoted as "Consensus-Adapted."

Recognizing the need to provide practical guidance for common problems that may lie outside of the panel's evidence reviews or available science, in many areas the published evidence was supplemented by the expertise of the panel members, who have many years of experience in managing and studying individuals with SCD. Recommendations based on the opinions of the expert panel members are labeled as "Consensus-Panel Expertise." Each is clearly labeled with the strength of the recommendation and the quality of evidence available to support it.

Determining the Strength of Recommendations

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework rates the strength of recommendations as "strong" or "weak." However, the panel modified the GRADE system and used a third category—moderate—when they determined that patients would be better off if they followed a recommendation, despite there being some level of uncertainty about the magnitude of benefit of the intervention or the relative net benefit of alternative courses of action. The panel intends for these moderate-strength recommendations to be used to populate protocols of care and provide a guideline based on the best available evidence. The panel does not intend for weak- or moderate-

strength recommendations to generate quality-of-care indicators or accountability measures or affect insurance reimbursement. Variation in care in the areas of weak- or moderate-strength recommendations may be acceptable, particularly in ways that reflect patient values and preferences. Conversely, strong recommendations represent areas in which there is confidence in the evidence supporting net benefit, and the recommendations likely apply to most individuals with sickle cell anemia. For more information, see the "Rating Scheme for the Strength of the Recommendations" field.

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Strong recommendation High-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies*	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation Moderate-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation Low-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation Very low-quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.
Weak recommendation High-quality evidence	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation Moderate-quality evidence	Benefits closely balanced with harms and burdens	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation Low-quality evidence	Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and burdens	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation Very low-quality evidence	Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain.

Source: Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med*. 2006 Sep 1;174(5):605-14. Official Journal of the American Thoracic Society.

*Exceptionally strong evidence from unbiased observational studies includes: (1) evidence from studies that yield estimates of the treatment effect that are large and consistent; (2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and (3) evidence in which a dose-response gradient exists.

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

Consensus–Panel Expertise

- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).
- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with sickle cell disease [SCD] presenting with fever or worsening anemia).
- Recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus–Adapted

- These recommendations were based on the panel's expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Prior to publication, these guidelines were reviewed by the National Heart, Lung, and Blood Institute (NHLBI) Advisory Council, a separate panel of sickle cell disease (SCD) experts, and the National Blood Disorders Program Coordinating Committee. The guidelines were also posted to the NHLBI Web site for an extensive public review and comment period, which resulted in the submission of more than 1,300 comments from individuals and professional societies. The expert panel and NHLBI staff reviewed each comment or recommendation, many of which resulted in a revision to the guidelines. The guidelines were then reviewed by SCD experts representing three professional societies.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Hydroxyurea can reduce the frequency of sickle cell-related pain and the incidence of acute chest syndrome (ACS).
- Although fetal hemoglobin (HbF) induction is the most powerful effect of hydroxyurea and provides the biggest direct benefit for people who have sickle cell disease (SCD), additional mechanisms of action and benefits exist. For example, hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters the expression of adhesion molecules, all of which contribute to vaso-occlusion. Hydroxyurea also raises red blood cell (RBC) volume (higher mean corpuscular volume [MCV]) and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion. In addition, nitric oxide released directly from hydroxyurea metabolism may contribute to local vasodilation.

Potential Harms

- Potentially unknown long-term adverse effects of hydroxyurea therapy
- Evidence of side effects of hydroxyurea in sickle cell anemia (SCA) is presented in Exhibit 13 in the original guideline document. Potential toxicity includes bone marrow suppression (reversible cytopenia). Numerous other side effects were reported in the literature with low frequency and none with certain causality. Minimal human data exist on potential harmful reproductive effects of hydroxyurea in males and females.

Contraindications

Contraindications

In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy.

Qualifying Statements

Qualifying Statements

The purpose of the "Evidence-Based Management of Sickle Cell Disease: Expert Panel Report (EPR), 2014" is to synthesize the available scientific evidence on sickle cell disease and offer guidance to busy primary care clinicians. Readers of this report should remember that this document is intended to provide guidance for management, not to be rigidly prescriptive. The panel recognizes that the responsible clinician's judgment regarding the management of patients remains paramount. Therefore, the Expert Panel Report is a tool to be adopted and implemented in local and individual settings, and to provide an opportunity for shared decisionmaking in which providers and patients are both fully engaged.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Hydroxyurea therapy in the management of sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 71-8.

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014

Guideline Developer(s)

National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]

Source(s) of Funding

United States Government

Guideline Committee

Expert Panel

Composition of Group That Authored the Guideline

Panel Members: George R. Buchanan, M.D. (*Co-chair*), University of Texas Southwestern Medical Center, Dallas, TX; Barbara P. Yawn, M.D., M.Sc., M.S.P.H. (*Co-chair*), University of Minnesota, Rochester, MN; Araba N. Afenyi-Annan, M.D., M.P.H., University of North Carolina at Chapel Hill, Chapel Hill, NC; Samir K. Ballas, M.D., Thomas Jefferson University, Cardeza Foundation, Philadelphia, PA; Kathryn L. Hassell, M.D., University of Colorado Denver, Aurora, CO; Andra H. James, M.D., M.P.H., University of Virginia, Charlottesville, VA; Lanetta

Jordan, M.D., M.P.H., M.S.P.H., Foundation for Sickle Cell Disease Research, University of Miami, Miller School of Medicine, Miami, FL; Sophie M. Lanzkron, M.D., M.H.S., Johns Hopkins School of Medicine, Baltimore, MD; Richard Lottenberg, M.D., University of Florida, Gainesville, FL; William J. Savage, M.D., Ph.D., Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Paula J. Tanabe, Ph.D., R.N., F.A.E.N., F.A.A.N., Duke University, Schools of Nursing and Medicine, Durham, NC; Russell E. Ware, M.D., Ph.D., Cincinnati Children's Hospital Medical Center, Cincinnati, OH; M. Hassan Murad, M.D., M.P.H. (*Methodologist*), Mayo Clinic, Rochester, MN

Refer to the original guideline document for members of the National Heart, Lung, and Blood Institute staff and the contractor support.

Financial Disclosures/Conflicts of Interest

The National Heart, Lung, and Blood Institute (NHLBI) established the expert panel and invited the panel members. All members served as volunteers and received no compensation from NHLBI or any other entity for their participation.

During the development of these guidelines, measures were taken to ensure the transparency of the evidence review process and to manage all potential or perceived conflicts of interest. At the initial expert panel meeting, expert panel members were asked by the panel co-chairs to disclose interests and relationships that could potentially influence their participation or pose a potential conflict of interest. The responses are provided below.

- Araba N. Afenyi-Annan, M.D., M.P.H.—Consultant, Transfusion Safety Summit: Risks Associated with Iron Toxicity in Transfusional Medicine—Novartis Pharmaceuticals Corporation (November 2008); Duke University Comprehensive Sickle Cell Center, Mentored Research Training Supplement (April 2005–April 2006); Expert Witness for Hall, Booth, Smith & Slover, P.C. (2010–present)
- Samir K. Ballas, M.D.—Speaker's Bureau, Novartis; Sickle Cell Advisory Board, HemaQuest; U.S. Sickle Cell Advisory Board, Sangart
- Kathryn L. Hassell, M.D.—Advisory Board, ApoPharma; Consultant, AGA Medical Corp.; Consultant and Principal Investigator of Local Site Multicenter Sickle Cell Study, Terumo, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, GlycoMimetics, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, Emmaus, Inc.; Board of Directors, Mount Evans Home Health & Hospice; Medical Advisory Board, Foundation for Women and Girls with Blood Disorders; Medical Advisory Board, PFO Research Foundation
- Andra H. James, M.D., M.P.H.—Consultancy for the von Willebrand Disease Medical Advisory Board for CSL Behring; Research study of antithrombin levels in pregnancy for Grifols/Talecris; Study of von Willebrand factor levels and fibrinogen levels post partum for CSL Behring; Expert witness for Johnson & Johnson and Sanofi-Aventis
- Lanetta Jordan, M.D., M.P.H., M.S.P.H.—National Heart, Lung, and Blood Advisory Council; Faculty Chair, Sickle Cell Disease Association of America, Inc. (SCDAA) and National Initiative for Children's Healthcare Quality (NICHQ) for Health Resources and Services Administration-funded Sickle Cell Disease Treatment Demonstration Program; AESRx Medical Advisory Council; Prolong Pharmaceutical Medical Advisory Board; Consultant for NKT Therapeutics, TriStem, Pfizer, and Novartis; Board Member, Foundation for Women and Girls with Blood Disorders and Miami YWCA
- Sophie M. Lanzkron, M.D., M.H.S.—Scientific Advisory Board for HemaQuest; Principal investigator on studies sponsored by Emmaus, GlycoMimetics, Inc., and Novartis
- Paula J. Tanabe, Ph.D., R.N., M.S.N., M.P.H.—Partner, ESI Triage Research Team, LLC; Principal investigator on Agency for Healthcare Research and Quality research grant; Subcontractor to the Michigan Public Health Institute and the Health Resources and Services Administration (HRSA) to conduct a project in SCD, pediatrics, emergency department (ED) research; recipient of Duke School of Nursing grant to complete a project to measure the effect of a high dose opioid protocol to treat adults with a vaso-occlusive crisis (VOC) in the ED; Expert witness consultant on one SCD legal case
- Russell E. Ware, M.D., Ph.D.—Consultant for Bayer, Novartis Pharmaceuticals, and Sobi

No relationships to disclose: George R. Buchanan, M.D.; Richard Lottenberg, M.D.; William J. Savage, M.D., Ph.D.; Barbara P. Yawn, M.D., M.Sc., M.S.P.H.

Guideline Endorser(s)

American Academy of Emergency Medicine - Medical Specialty Society

American Academy of Pediatrics - Medical Specialty Society

American Academy of Physician Assistants - Professional Association

American Osteopathic Association - Professional Association

American Society of Hematology - Medical Specialty Society

American Society of Pediatric Hematology/Oncology - Professional Association

International Association of Sickle Cell Nurses and Physician Assistants - Professional Association

National Black Nurses Association, Inc - Professional Association

National Institute for Children's Health Quality - Professional Association

National Medical Association - Professional Association

Sickle Cell Disease Association of America - Disease Specific Society

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [National Heart, Lung, and Blood Institute \(NHLBI\) Web site](#) .

Print copies: Available from the NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: [nhlbic@dgsys.com](mailto:nhlbiic@dgsys.com)

Availability of Companion Documents

The following are available:

- Evidence-based management of sickle cell disease. Expert panel report quick guide. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. 45 p. Electronic copies: Available from the [National Heart, Lung, and Blood Institute \(NHLBI\) Web site](#) .
- Management of sickle cell disease. Summary of the 2014 evidence-based report by expert panel members. JAMA. 2014 Sep 10;312(10):1033-1048. Electronic copies: Available from the [Journal of the American Medical Association \(JAMA\) Network Web site](#) .
- Murad MH, Hazem A, Shahrour A, Prokop L, Lane M, Mullan R, Elraiyah T, Montori VM. Hydroxyurea for sickle cell disease: a systematic review of benefits, harms, and barriers of utilization, 2012. 116 p. Electronic copies: Available from the [NHLBI Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 24, 2014.

Copyright Statement

No copyright restrictions apply.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouse^{â„¢} (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the [NGC Inclusion Criteria](#).

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.